REMARKS

Claims 23 and 32-46 are pending. Applicants respectfully request reconsideration and allowance of claims 23 and 32-46 in view of the following remarks.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 23, 32-33, 35, 37-40, and 42 under 35 U.S.C. § 102(b) over Sanders *et al.*, U.S. Pat. No. 5,766,605. The Examiner asserted that "there does not appear to be any unexpected results when the composition of botulinum toxin, local anesthetic and vasoconstrictive agent is admixed in a container immediately prior to use." The Examiner also asserted that "the fact that applicant has recognized another advantage which would flow naturally from following the suggestions of the prior art cannot be the basis for patentability when the differences would otherwise be obvious."

As indicated in §2131 of the MPEP, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. V. Union Oil C o. of C alifornia*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The Sanders *et al.* patent does not disclose the articles of manufacture of claims 23, 32-33, 35, 37-40, and 42, which include an admixture of a botulinum toxin and either a local anesthetic agent or a local vasoconstrictive agent, or both. Rather, the Sanders *et al.* patent discloses a method for the control of autonomic nerve function that involves administering a therapeutically effective amount of botulinum toxin such that denervation of the neurons is achieved. In the cited passage of the Sanders *et al.* patent (column 8, lines 21-31), a sedative, a decongestant, a local anesthetic, and botulinum toxin were sequentially administered. Sequential administration of a botulinum toxin, a local anesthetic, and a local vasoconstrictive agent does not teach an article of manufacture comprising an admixture of a botulinum toxin and either a local anesthetic agent or a local vasoconstrictive agent, or both. Thus, the Sanders *et al.* patent does not anticipate claims 23, 32-33, 35, 37-40, and 42.

Furthermore, the Sanders *et al.* patent does not teach or suggest an article of manufacture as recited in claims 23, 32-33, 35, 37-40, and 42. Instead, as discussed above, the Sanders *et al.* patent provides a method for the control of autonomic nerve function. In the cited passage of the

Sanders *et al.* patent (Example IV, column 8, lines 21-37), experiments were done to confirm that botulinum toxin is an effective long-term therapy for vasomotor rhinitis, which is characterized by "a copious flow of clear, watery secretions" that result from excessive parasympathetic activity. See column 1, lines 37-41 and column 7, lines 22-26 of the Sanders *et al.* patent.

In contrast to the Examiner's assertions, the cited passage does not teach or suggest a composition comrpsing a vasoconstrictor, lidocaine, and botulinum toxin. Sanders *et al.* simply applied the decongestant to clear the nasal passages and applied the local anesthetic to prevent autonomous effects on the nasal mucosa by mechanical irritation. See column 8, lines 61-65 of the Sanders *et al.* patent, which indicate that topically anesthetizing the nasal mucosa relieves the sensation of nasal obstruction, but does not change nasopulmonary airway resistance. Sanders *et al.* overall conclusion is that rhinorrhea and other disorders associated with control of autonomic nerve function can be treated by locally administering botulinum toxin. Sanders *et al.* do not suggest combining botulinum toxin in a composition with either a local vasoconstrictor or local anesthetic, or both.

Even if sequential administration did result in the formation of such a composition in the dog's nasal passages, the fact that Sanders *et al.* disclose separate administrations of each composition over a 10 minute time lag teaches away from an article of manufacture comprising an admixture of the three components for simultaneous administration. In light of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. §103

The Examiner rejected claims 23 and 32-46 under 35 U.S.C. §103(a) over Adams et al. (U.S. Patent No. 4,029,794) in view of Sanders et al. (U.S. Patent No. 5,766,605). The Examiner asserted that Adams et al. does not teach botulinum toxin and Sanders et al. does not teach the vaasoconstrictor epinephrine. The Examiner asserted that it would be prima facie obvious to substitute botulinum toxin for saxitoxin and epinephrine for phenylephrine given the "reasonable

expectation that the respective species will behave in a comparable manner or give comparable resutls in comparable circumstances as noted in Sanders et al." Applicants respectfully disagree.

Adams *et al.* teaches a local anesthetic composition that includes a mixture of saxitoxin and a conventional local anesthetic compound. Applicants submit that it is not obvious to "substitute the neurotoxin botulinum toxin for the neurotoxin saxitoxin." Saxitoxin and botulinum toxins have different sites and mechanisms of action. Saxitoxin alters the action potential at the voltage-gated sodium channels along the neuron axon and is used for nerve blocks to induce local anesthesia. See, Watters (1995) *Clin Neurol Neurosurg* 97:119-124 (reference AQQ of the Form 1449 submitted June 17, 2002). In contrast, botulinum toxins block the release of acetylcholine at the neuromuscular endplate of neurons and are used to induce paralysis. See, specification at page 6, lines 13-14 and Schantz *et al.* (1992) *Microbiol Reviews* 56:86-99 (reference AHH of the Form 1449 submitted June 17, 2002).

Saxitoxin and botulinum toxins also have different pharmacokinetic properties. As indicated in the specification, the paralysis induced by saxitoxin does not last as long as the paralysis induced by botulinum toxin, and repeated injections of saxitoxin would be needed. See, for example, the specification at page 7, lines 22-25. Also see Kohane *et al.*, (2000) *Reg Anesth Pain Med* 25(1):52-59 (reference ARR of the Form 1449 submitted June 17, 2002), which indicates that the duration of action of saxitoxin is only a few hours. Furthermore, while saxitoxin may be used as a local anesthetic, the effective dose of saxitoxin is relatively close to the lethal dose in animals. See, Schantz *et al.*, *supra*. As indicated in Adams *et al.* and in Schantz *et al.*, *supra*, small amounts of saxitoxin can be mixed with a local anesthetic, which results in a composition that has unusually greater anesthetic effects. The amount of saxitoxin in such compositions (e.g., 1 part saxitoxin per 10,000 parts local anesthetic), however, does not induce paralysis. See, page 92 of Schantz *et al.*, *supra*. Since saxitoxin and botulinum toxins have different sites of action, different mechanisms of action, and different pharmacokinetic properties, the two neurotoxins cannot simply be substituted for one another as there is no reasonable expectation that the two neurotoxins will behave in a comparable manner or give comparable results in comparable circumstances.

The Sanders *et al.* patent does not remedy the deficiencies of the Adams *et al.* patent. As described above, the Sanders *et al.* patent provides a method for the control of autonomic nerve function. The Sanders *et al.* patent does not teach or suggest an article of manufacture containing admixtures of a botulinum toxin and either a local anesthetic agent or a local vasoconstrictive agent, or both. Therefore, the articles of manufacture are non-obvious in view of the cited art. Applicants request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a).

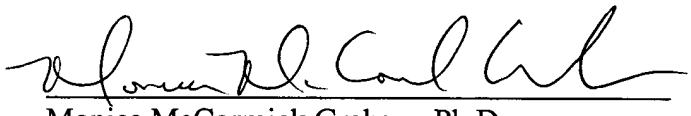
CONCLUSION

Applicants respectfully assert that the pending claims are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned agent if such would expedite prosecution.

No extension fees are due as this response is being filed before the end of the shortened statutory period. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 4/15/04



Monica McCormick Graham, Ph.D.
Reg. No. 42,600

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696